

The Brain in Pain: A Review of Nociception and Advancements in the Study of Chronic Pain

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Abstract

Pain perception is different for everyone; however, one similarity for all people who suffer from chronic pain is that it decreases their quality of life. Research has shown that the subjectivity of pain is caused by different psychological aspects such as cognition, context, and emotion. These characteristics control neural processes that control pain perception. Different research paradigms using these psychological features have led scientists to conclude that the prefrontal cortex plays a vital role in pain perception. Furthermore, a link has been made between the neural processing of nociception and the neural processing of reward. While this relationship is critical for survival because it leads to an avoidance of dangerous stimuli, it also proves to be problematic in the treatment of pain because current medications that reduce pain also result in addiction. This tethering of pain relief with addiction suggests a need for therapies that do not alter the reward circuitry. One target for this purpose is the prefrontal cortex because of the integral role it has shown to play in chronic pain. To investigate this, experiments have been created to enable the exploration of electrophysiological and morphological plasticity in neurons from the prefrontal cortices of animals. A better understanding of cellular adaptations that occur in the prefrontal cortex as a result

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of pain could lead to therapies that are better suited for treating this condition.

The experience of pain is multi-faceted. According to the International Association for the Study of Pain, pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” This definition suggests that pain is not based solely on an unpleasant sensation caused by a stimulus but is also based on psychological characteristics that are unique to each individual. The multiple psychological aspects that control an organism’s perception of pain include individual memories, attention, mood, and genetics. As Tracey argues, these influences make pain a subjective experience that is unique to the organism and the context of each pain experience (109). In conjunction with the psychological aspects that control pain perception, there is a widely distributed neural network that modulates pain. While the multiple aspects and complex brain circuitry complicate the understanding and study of pain perception, they also offer multiple novel treatment targets for what is a serious public health problem.

There is a strikingly high prevalence of chronic pain in the population. According to a review by Tracey and Mantyh, approximately twenty percent of the adult population suffers from chronic pain that originates from multiple pathologies; the main sufferers are women and the elderly (377). Not only is pain influenced by the emotional condition of the patient, but it also takes a heavy emotional toll on the patient as well as caretakers. In addition to the physical and psychological handicaps of chronic pain, it also creates a financial burden. People suffering from chronic pain experience a loss in productivity, which usually makes it difficult for them to hold jobs. While many receive some support from the government, their lives are much more difficult as a result of their condition. The high prevalence and oppressing effects of chronic pain, which is more and more becoming accepted as a disease, make it an important area of study.

In the study of pain, it is important to distinguish between acute pain and chronic pain because these two conditions have different effects on the brain. Acute pain is pain that is experienced for a short period of time, such as what is experienced following surgery. It has been studied extensively in animals as well as people, and the neural

mechanisms that translate the noxious stimulation in the periphery to the nociception, or neural encoding of the stimuli in the brain, are fairly well-understood. Because of this understanding and the short-term nature of acute pain, there are successful treatments for it. In contrast, chronic pain is pain that subsists for three months or longer such as what is experienced due to nerve damage or arthritis. The long-term nature of chronic pain increases its influence on neural circuitry and makes it more difficult to treat (Tracey and Mantyh 377-78). The brain changes in response to acute pain; however, acute pain is quickly over and these changes do not last. When chronic pain occurs, the prolonged activation in pain neural pathways causes permanent changes, and these changes diminish the body's capacity to cope with the pain endogenously as well as with available medication. An understanding of where and how these changes take place could lead to a way to reverse these changes and relieve chronic pain. The lack of information and available treatments for chronic pain suggests the necessity for basic and clinical research in this area in order to improve the lives of countless people.

An understanding of the basic mechanism that occurs during acute and chronic pain is important for studying the plasticity (changes in synaptic strength) that results from chronic pain. In the pain network, information ascends from the site of the noxious stimulus to many structures in the brain. These structures then descend back down in a feedback loop that influences the ascending information and subsequently alters perception. First in this process, a noxious stimulus activates nociceptors, which are sensory receptors located in the periphery that detect potentially damaging stimuli. From there, the information is relayed to the dorsal horn of the spinal cord where it crosses to the side of the body that is contralateral to the site of the stimulus. In layer II of the dorsal horn of the spinal cord, the pain signal travels to the brain where it is transmitted through multiple tracts. The tract most appropriate for pain research is the spinothalamic tract (STT) because structures along this tract have been shown to be responsible for encoding the intensity of the pain experienced. Neurons in this tract synapse in the rostroventromedial (RVM) medulla and the periaqueductal grey (PAG) in the brainstem, the amygdala, and higher brain structures in the cortex. This ascending activation, which

is caused solely by sensory information, is influenced by a descending regulatory pathway. Due to modulation by this descending pathway, pain is a unique experience that is altered by context, cognition, and emotion. These factors influence the cortical structures involved in pain processing, and these cortical structures subsequently affect brainstem activity. This interaction can activate or inhibit the activity in the RVM medulla and PAG, which then alters the ascending flow back up to the cortical structures (Tracey and Mantyh 378-80). The effects that top-down aspects have on the descending pain network and the experience of pain suggest how pain can be altered, and they provide insight into treatment techniques.

Psychological factors that control pain as well as current drug treatments for pain act on the brainstem structures in the pain pathway. These structures are dense with opioid receptors, and the activation of these receptors modulates perception. As Basbaum and Fields established long ago, opioid receptors in the RVM medulla and PAG are activated by endogenous opioids called endorphins. Binding of endorphins to these receptors causes an inhibition of the pain signal. Cortical structures control the release of endorphins in the brainstem, and this control is influenced by psychological factors. This means that psychological factors that influence cortical structures can cause an attenuation or inhibition of the pain signal based on their influence on the release of endorphins (451-52). Endogenous opiates can inhibit the pain signal, but synthetic opiates such as morphine control pain more adequately than the endogenous system through the same mechanism; however, as suggested by Field, opiates have been shown to be highly addictive when taken for long periods of time (591). This association of pain treatment and addiction suggests a larger systems tie between pain circuitry and reward circuitry in the brain. It certainly indicates a need for chronic pain treatments that do not pose a risk for addiction.

There have been extensive human imaging studies in order to establish the structures that are a part of the pain network and to determine the role that they play. The many factors that have an effect on pain perception such as cognition, context, and mood have been linked to discrete structures in this large and spread-out network in the brain that encodes a painful stimulus and modulates its perception. As described by Tracey and Mantyh, a study using positron emission

tomography (PET), functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG) established that primary and secondary somatosensory cortices, insular, anterior cingulate cortex (ACC), prefrontal cortex (PFC), and thalamus are commonly activated in addition to brainstem structures during an acute pain experience (379). The psychological aspects of pain have been extensively explored by examining their effects on these areas using human neuroimaging and various paradigms.

Pain is dramatically influenced by the cognitive state of the person experiencing pain. Cognition refers to the processing of information; in this case, the degree to which a person attends to pain. For example, a person's pain experience is much more severe if he or she is being hyper-vigilant to the pain as compared to if he or she is ignoring it. In their review, Wiech, Ploner, and Tracey have described paradigms that are used to explore why this occurs. While pain is something that is inherently difficult to ignore, differences were seen when a certain level of distraction was achieved. Distraction tasks resulted in a greater activation in the PFC, ACC, and PAG. Specifically, changes in activation in the PFC and ACC caused the greater activation of opioid receptors in the brainstem. Thus, distracting tasks cause activation of the descending pathway which results in a reduction of pain. Conversely, while it has not been definitively proven, it is thought that hyper-vigilance, which is common among chronic pain patients and has as grave influence on the quality of life, decreases activation of the descending network which subsequently decreases endogenous opioid activation in the brainstem and attenuates the pain signal (306). This human imaging study shows that top-down cognitive influences change the experience of pain by altering the descending regulatory network and offers the PFC and ACC as areas of interest for treatment targets.

Building on the influence of cognition on the top-down pathway, the context of pain has been shown to have similar effects. Context refers to a person's beliefs or expectations, which are greatly influenced by past experiences. Tracey and Mantyh show that the effects of context on pain can be explained through the placebo effect as well as the effects of a person believing his or her pain is far more dangerous than it actually is. Often when people expect to feel better they do,

even if there is no physiological explanation. The expectation that pain will be improved, implicated by a placebo, causes changes in the hypothalamus, amygdala, ACC, insular, and PFC. Molecular imaging techniques have shown that these changes occur along with an increase in activity in opioid receptors in the brainstem, which indicates that activation in these cortical structures activates the descending pain pathway and thus modulates pain. Alternately, catastrophizing, or experiencing anxiety due to the belief that pain felt is more dangerous than it actually is, causes a reduction in this pathway and subsequently an attenuation of the pain signal (381-82). The influence of context on the descending pain pathway and the neurological mechanism by which this occurs further implicates the PFC and ACC as valuable areas to target for pain treatment.

In addition to cognition and context, a person's emotions have been shown to have an effect on pain processing; however, there is not an established systems understanding of this modulation. It is known that anticipation, anxiety, and depression result in a heightened pain experience. This heightened pain experience is linked to changes in dopaminergic transmission from the ventral tegmental area as well as changes in the medial PFC (Tracey and Mantyh 382-83). Along with a further implication of PFC modulation being crucial in pain perception, this emotional aspect of pain additionally links the pain circuitry with reward circuitry.

There is a large amount of evidence to suggest that the prefrontal cortex is important for modulating pain and that it plays a role in chronic pain. There is a pronounced PFC activation in all clinical pain states, no matter the pathology of origin, and the degree of this activation has been shown to correlate with the intensity of the pain experienced. Furthermore, neuroimaging of chronic pain patients has shown that neurodegeneration occurs in the dorsolateral PFC in the chronic pain state. This neurodegeneration could result from multiple origins, one of which is excitotoxicity, or cell death due to over activation of cells by an excitatory neurotransmitter such as glutamate. This neurodegeneration could result in less of a modulation on the descending pathway by the PFC, which deregulates the body's mechanism to inhibit pain (Tracey and Mantyh 383-84). The activation of the prefrontal cortex by pain and the factors that affect pain as well

as the linkage to the PFC to another important network make it a very appealing area to study for specific cellular changes in the chronic pain state.

The coupling of opiate drugs with addiction, the modulation of pain by emotion, and the role of the PFC in pain all tie the mesolimbic dopamine pathway, which is responsible for reward and motivation, to pain. The mesolimbic dopamine pathway begins in the ventral tegmental area (VTA). From this area, dopaminergic neurons project to glutamate neurons in the PFC, GABA neurons in the nucleus accumbens core, and glutamate neurons in the basolateral amygdala. In addition to the projections from the VTA to these cortical structures, the PFC and nucleus accumbens project back onto the VTA, and neurons from the PFC project to the nucleus accumbens. According to Kalivas and Volkow, alterations in this mesolimbic pathway, specifically an increase in dopamine transmission, result in a change in behavior that indicates an increased motivation for a cue (1404). In addition to changes in the PFC seen in the pain state, Scott et al. have shown that pain causes changes in dopamine transmission; however, it is unclear if the PFC causes changes in the VTA or if changes in the VTA causes changes in the PFC (10789). This covariance in the VTA and PFC ties together the circuitry responsible for pain and pleasure and is a valuable area for study in pain models.

There have been many animal studies done to understand the role of dopamine transmission in chronic pain, most of which have altered the amount of dopamine available in the mesolimbic pathway. Altier and Stewart have described experiments where lesions of dopaminergic neurons have been created in rats using 6-hydroxydopamine (OHDA). These animals showed to have a greater sensitivity to pain, suggesting that a decrease in dopamine transmission could lead to chronic pain. Conversely, they have described that dopamine agonists result in pain relief. When injected with apomorphine or psychostimulants such as cocaine and heroin, all of which are addictive because they dramatically increase dopamine transmission, the animals experienced analgesia (2269). This coupling of pain relief with dopamine agonists is logical because opiates, drugs that dramatically reduce pain, are dopamine agonists. It is highly likely that their mode of action is not solely by activating opioid receptors in the brainstem (and thus controlling

the descending pathway) but also by causing a release in dopamine. More specific roles for dopamine were discovered by Potvin, Grignon, and Marchand through the use of antipsychotics, which are D2/D3 dopamine receptor antagonists. When these antagonists are used, the animal no longer experiences pain relief from amphetamine or morphine. This suggests that D2/D3 receptors are important in achieving analgesic effects with dopamine (390).

In addition to animal studies, human studies have been carried out to explore the correlation of dopamine activity with emotion and how that may act to change pain perception. One study explored the role of D2/D3 receptors in striatal and mesolimbic pathway neurons. This study showed that changes in D2/D3 receptors activation correlated with changes in the perceived unpleasantness, what is called the affective component, and fear of the pain. Specifically, less D2/D3 receptor availability in the nucleus accumbens was correlated to an increase in the affective component of the pain. Because D2/D3 receptors cause an inhibitory G-protein cascade, a reduction of these receptors results in a reduction of inhibition in the nucleus accumbens. This reduction is a possible mechanism by which the affective component of pain, an emotional element, modulates pain perception (Scott et al. 10789).

As noted by Leknes and Tracey, survival instincts of an organism promote the pursuit of pleasure and the avoidance of pain; therefore, these two tasks compete for importance in the brain. Because of this, it is logical that pain causes changes in both the pain and reward systems. It is also logical that medications that result in pain relief also result in addiction because of the dramatic increase of activity in the reward system. The relief of pain is a reward in itself. The more threatening a stimulus such as pain is to an organism, the more pleasure that organism will experience when that pain is relieved and homeostasis is reestablished. Oppositely, an organism can tolerate a small amount of pain if the end result is a reward; however, this link provides a huge problem in pain relief treatments because of the current inability to uncouple pain treatment with addiction (314). This uncoupling is a main goal in current pain research.

The PFC has proven to be a very important structure in the study of pain. As previously mentioned, changes in the PFC have been linked to the intensity of pain experienced in the chronic pain state.

It is also important because it is a structure that is present in both the mesolimbic pathway and the pain pathway. Cellular studies in the PFC could provide evidence of novel ways to treat pain that do not result in addiction, and these cellular studies require valid animal models. There are two models for chronic pain in rats that provide a high degree of validity to the overarching problem of chronic pain.¹ In addition, when used together these models allow the insurance that the adaptations seen are common to chronic pain in general rather than one specific kind of chronic pain. Chronic pain comes in many forms. Persons with back pain, fibromyalgia, and osteoarthritis are all in chronic pain; however, the pain stems from different origins. While the genetic factors contributing to chronic pain have been studied, Mogil has noted that there are far too many that combine to create the chronic pain state to be used as a model (283); therefore, chemical and surgical methods must be used to create a model in non-human species, and factors such as sex, genotype, and social communication must be held constant because of all of the top-down processes that influence pain. One model is the intraplantar injection of complete Freund's adjuvant (CFA). This model results in chronic inflammatory pain, which is pain similar to that suffered from rheumatoid arthritis. Another model for chronic pain is the spared nerve injury (SNI). This is similar to neuropathic pain. Both models have strengths and weaknesses, and a combination of both is the best method for chronic pain research.

CFA is a suspension of *Mycobacterium tuberculosis*, which causes an immune-reaction and results in inflammation at the site of injection. This immune reaction creates allodynia, or an increase in sensitivity to non-noxious stimuli, on the ipsilateral paw of a rat. While the use of CFA is unethical and legally forbidden for human studies, one accidental injection into a human finger has provided an account of the pain experienced following a CFA injection. Approximately ten hours after the inadvertent injection, the investigator (Gould) felt moderate discomfort because of an increase in pressure at the injection site. He described a burning sensation twenty hours after the injection. The investigator began to guard the injected digit in order to keep away from stimulation. The discomfort mainly due to mechanical stimulation decreased slowly but persisted for approximately 42 days (301). The accidental injection of this investigator provides efficacy to the CFA

model because it provides insight into the discomfort experienced and provides a time-frame. The effects of CFA last for a relatively long time, making it valid for chronic pain; however, inflammation has many complexities and could therefore cause greater activation in the brain than general pain. This is why the SNI model should be used in conjunction with the CFA model.

Another model for pain is the spared nerve injury (SNI), which is described by Decosterd and Woolf. This involves performing a blunt dissection into the hind limb of a rat in order to reveal the sciatic nerve. This nerve branches into three: the tibial, common peroneal, and sural nerves. The tibial and common peroneal are ligated together in two places, and an approximately three millimeter piece of the nerves is removed. The sural nerve is left intact. The dermatome on the paw on the ipsilateral side that corresponds to the area that the sural nerve innervates becomes hypersensitive following this procedure. This procedure has an almost immediate effect, and the effect is sustained for long periods of time, up to 220 days or longer; therefore, SNI provides a valid model for chronic neuropathic pain (149-50).

In addition to pain models needed to create pain, ways to measure the intensity of the pain that the animals experience is important. A method is described by Chaplan et al. that uses von frey filaments, which are small plastic fibers that deliver a certain pressure to a defined area. Rats are put into small chambers that have a mesh floor so that their paws are exposed. The filament is applied to the area of the paw made sensitive by CFA or SNI. A very small pressure is first applied, and this pressure is increased until a positive response, the rat lifting its foot, occurs. Using a series of responses from different qualities of stimuli, the rat's pain threshold can be calculated (55). A marked decrease in pain threshold, which is correlated to an increase in the pain experienced, occurs when both models, CFA and SNI, are employed.

From these pain models, multiple studies can be done to explore pain through plasticity in the PFC. This plasticity can be explored through the use of electrophysiology and imaging of neuronal structure. The PFC is composed of glutamatergic pyramidal neurons. Metz et al. have investigated the morphological and electrophysiological changes in medial PFC pyramidal neurons following SNI. Their study showed that one week following surgery, there was a significant difference

between SNI and sham-operated animals (animals that undergo a surgery in which their sciatic nerve is exposed but not removed). Electrophysiological recordings showed that excitatory post synaptic currents in SNI animals were mediated much more by NMDA channels as opposed to AMPA channels, whereas in sham animals the activity through these two types of sodium channels was roughly equal. In addition, there were morphological changes in PFC neurons. Here, they showed that the basal dendrite on the pyramidal neurons was longer, more branched, and contained more spines in an SNI operated animal compared to sham. They observed no changes in apical dendrites (2424-26). From this study, much can be done to expand on knowledge about plasticity that occurs in the PFC in response to pain and ways in which this can be reversed.

There is still much to learn about the morphological and electrophysiological plasticity that occurs in the PFC as a result of chronic pain. For example, SNI and CFA models should be employed together to ensure that any responses observed are common to all types of chronic pain. In addition, these models should be used for various amounts of time to see how chronic pain causes changes over time. Patch clamp recordings can be used to ascertain any other changes in currents that occur, and different drugs can be applied to see if these changes can be reversed. Similarly, morphological changes can be observed over time, and drugs can be given systemically and intracranially to see if they can reverse the changes. A continuation of this work could lead to advancement to a treatment that adequately treats pain without causing addiction.

Chronic pain is a serious disease, and there are currently no practical therapies to treat it. Clinical research using neuroimaging to evaluate areas of the brain that are activated under different conditions in the pain state have moved this field forward by suggesting areas that must be targeted. From there, basic research must continue to pin down the cellular adaptations that occur as a result of pain. This can be done through electrophysiological and morphological evaluation of neurons in areas known to be altered by chronic pain; the most prevalent area to see such changes is the prefrontal cortex. With more knowledge about these cellular changes, new therapies can be developed that do not upset the balance between the pain and reward circuitry. In order

to alleviate peripheral chronic pain for those who suffer from it, the cellular changes must be reversed; in order to block chronic pain in the periphery, its effects on the brain must be addressed.

Notes

¹The welfare of animals used in research is not only a top priority of investigators; it is also a top priority of research institutions. For that reason, animal research is highly regulated by institutional animal care and use committees set in place by the institutions. In all animal research and especially research studying pain, there is an effort to minimize the number of animals used to produce valid results. Investigators must show to the animal use committee that there is no alternative method to study each topic. Further, investigators make efforts to minimize the amount of suffering experienced by the animals. Animals that exhibit symptoms that their pain is more severe than allodynia (hypersensitivity in a specific area) are treated for that pain or euthanized. Every effort is made to reduce suffering of animals while also making progress towards treating serious public health problems.

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